

## Effect of *Haemophilus influenzae* Infection and Moxalactam on Platelet Function in Children

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**In a prospective randomized study, children with *Haemophilus influenzae* type b meningitis received (i) moxalactam or (ii) ampicillin or chloramphenicol. Of 41 children, 6 had prolonged bleeding times (>6 min), and 7 of 9 tested had abnormal platelet aggregation at hospital admission. At the end of therapy, no children in the ampicillin-chloramphenicol group, compared with 5 of 22 moxalactam-treated children (23%) ( $P = 0.08$ ), had prolonged bleeding times (6.5 to 7.5 min). Our data suggest that *H. influenzae* meningitis and treatment with moxalactam may each have an effect on platelet function in children.**

Bleeding associated with the administration of moxalactam is related to vitamin K-dependent hypoprothrombinemia, as well as platelet dysfunction (2, 9). Prolonged bleeding times and abnormal platelet aggregation have been described for adults who have received high dosages of moxalactam, and almost all cases of hemorrhage associated with moxalactam have been reported for adults (12, 14). No serious bleeding disorders have been reported in the United States for children treated with moxalactam for a wide variety of infections (5, 7, 8, 10). However, serious bleeding was reported for two children with meningitis treated with moxalactam in Hong Kong (4).

The effect of moxalactam on platelet function in children has not been evaluated. Therefore, we included such a study as part of an ongoing prospective comparative trial.

Children who were 2 months of age or older admitted to Texas Children's Hospital with *Haemophilus influenzae* type b meningitis were randomized to receive moxalactam (200 mg/kg per day in four divided doses), ampicillin (300 mg/kg per day in six divided doses), or chloramphenicol (100 mg/kg per day in four divided doses) for at least 10 days intravenously (8). Children treated with ampicillin and chloramphenicol, which were administered to the same patients only briefly (i.e., until organism identification), were considered as one group for comparison to moxalactam. Vitamin K (5 to 10 mg) was administered once parenterally at the beginning of therapy to children randomized to moxalactam. Parents were questioned carefully concerning the medications (particularly aspirin or aspirin-containing products) their children were receiving before admission. No child received aspirin in the hospital.

Complete blood counts and platelet counts were obtained at admission and at the conclusion of therapy. A modified Ivy test for bleeding time was performed by trained technicians within hours after admission of the patients to the hospital but after Vitamin K administration and at the end of antibiotic therapy. The average of two determinations was recorded as the bleeding time. The test was not considered valid if the two determinations differed by greater than 3 min. The normal bleeding time by the Ivy test is between 1 and 6 min in our institution.

Platelet aggregation was determined by standard techniques with ADP at final concentrations of 5 and 10  $\mu$ M (3).

Aggregation was expressed as percent maximal aggregation and aggregation at 10 min, a measure of platelet disaggregation. Day-to-day variation for percent maximal aggregation on the same normal individual is  $\leq 5\%$ .

Statistical analysis of the data was performed with the paired *t* test and Fisher exact test.

Altogether, 22 children were treated with moxalactam, 13 were given ampicillin, and 6 were treated with chloramphenicol. The mean age  $\pm$  standard deviation of the children in the moxalactam group was  $14.9 \pm 12.1$  months (excluding two children 9 and 14 years old), compared with  $12.9 \pm 9.7$  months for the ampicillin-chloramphenicol group. Children in both treatment groups had significantly ( $P < 0.001$ ) greater platelet counts at the end of therapy than at admission. Only one child in either group had an initial platelet count less than 100,000/ $\mu$ l. At the end of therapy, thrombocytosis ( $>750,000/\mu$ l) was noted for 10 of 18 children in the ampicillin-chloramphenicol group and 10 of 21 in the moxalactam group ( $P = 0.81$  by the Fisher exact test).

On admission, 3 of 17 children in the ampicillin-chloramphenicol group with platelet counts performed had prolonged bleeding times of 6.5, 7.5, and 10 min when their platelet counts were 158,000, 312,000, and 269,000/ $\mu$ l, respectively. A fourth child had a mildly prolonged bleeding time (7.0 min) on admission but had received aspirin before admission and had an initial platelet count of 74,000/ $\mu$ l. Of 21 children in the moxalactam group at admission, 3 had prolonged bleeding times of 8.5, 9, and 10 min when their platelet counts were 182,000, 138,000, and 130,000/ $\mu$ l, respectively. One additional child who received aspirin before admission had an initial platelet count of 241,000/ $\mu$ l and a bleeding time of 14.5 min.

At the end of therapy, all children in the ampicillin-chloramphenicol group had bleeding times that were within the normal range. Of the 22 children in the moxalactam group, 5 (23%) had prolonged bleeding times at the end of therapy ( $P = 0.08$ ). In four of the five children, the bleeding times were only mildly abnormal (6.5 to 7.5 min). The fifth patient (the child who had received aspirin before admission) had a bleeding time of 16 min at discharge. All children in both groups had platelet counts greater than 250,000/ $\mu$ l at the end of therapy.

Only 2 of 9 children on admission had maximal aggregation greater than 50% stimulated by 5 or 10  $\mu$ M ADP (Table 1). The same two patients were the only children to have

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TABLE 1. Platelet function tests in children with *H. influenzae* type b meningitis<sup>a</sup>

Drug treatment and patient no.	Patient age	Platelet functions at:							
		Admission to hospital				End of therapy			
		Platelet count/ $\mu$ l	Bleeding time (min)	Maximal aggregation (%) <sup>b</sup>	10-min aggregation (%) <sup>b</sup>	Platelet count/ $\mu$ l	Bleeding time (min)	Maximal aggregation (%) <sup>b</sup>	10-min aggregation (%) <sup>b</sup>
Moxalactam									
1	6 mo	397,000	3.0	31.3	16.7	863,000	3.5	12.2	0
2	14 mo	352,000	3.0	19.0	10.0	1,442,000	3.5	18.0	0
3	28 mo	182,000	8.5	19.7	14.1	695,000	6.0	7.0	2.4
4	9 yr <sup>c</sup>	130,000	10.0	31.8	12.4	556,000	4.0	44.3	13.2
5	14 yr <sup>c</sup>	261,000	4.0	65.5	61.0	276,000	7.0	12.2	2.2
Chloramphenicol									
6	4 mo	321,000	3.5	67.1	61.4	1,033,000	4.0	63.3	61.1
7	6 mo	269,000	10.0	43.4	26.6	830,000	2.5	24.4	17.4
Ampicillin									
8	12 mo	312,000	7.5	24.8	14.8	795,000	4.5	32.3	8.6
9	22 mo	158,000	6.5	27.6	23.6	657,000	3.0	16.7	1.5

<sup>a</sup> Only 5  $\mu$ M ADP data are shown because there was no difference with a 10  $\mu$ M concentration.

<sup>b</sup> In 10 normal adult volunteers, the mean percentages  $\pm$  standard deviations of the maximal platelet aggregation and aggregation at 10 min were  $71.7 \pm 10.4\%$  (range, 52.5 to 87.5%) and  $69.0 \pm 10.3\%$  (range 51 to 87%), respectively. In 10 term infants, the means of the maximal platelet aggregation and aggregation at 10 min were 77.1% (range 57 to 83%) and 75.1% (range 57 to 81%), respectively. Mean percentages  $\pm$  standard deviations of maximal platelet aggregation for the patients described above were  $34 \pm 2\%$  (at admission) and  $19 \pm 15\%$  (after therapy) for those treated with moxalactam and  $41 \pm 19\%$  (at admission) and  $34 \pm 20\%$  (after therapy) for those receiving chloramphenicol and ampicillin.

<sup>c</sup> Salicylate was detectable at  $<1.0$  mg/dl.

secondary platelet aggregation waves. At the end of therapy, only one child (child 6) demonstrated maximal aggregation greater than 50% and a secondary wave of platelet aggregation. Additional ADP up to a 100  $\mu$ M concentration did not result in further platelet aggregation in selected specimens.

No child in this study or in our combined studies with moxalactam for the treatment of *H. influenzae* type b meningitis (total of 131 children, 66 treated with moxalactam) had significant bleeding.

Moxalactam inhibits ADP-induced platelet aggregation in adults, possibly by interacting with the platelet membrane to alter ADP receptors. In adult volunteers, 12 g of intravenous moxalactam per day resulted in a progressive decrease in ADP-induced platelet aggregation, which occurred within 24 h of administration and reached its lowest point on days 6 and 7 of administration (2). In three additional adult volunteers receiving 12 g of moxalactam per day, bleeding times were prolonged to greater than 20 min by day 5 or 8 of administration (N. U. Bang and C. S. Harms, Program Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1063, 1983). Other  $\beta$ -lactam antibiotics also may impair platelet function by similar mechanisms (1, 3).

We found that after 10 days of therapy with the children, moxalactam administered at a dose that is greater per kilogram than that administered to adult volunteers was associated with mild prolongation of the bleeding time ( $\leq 7.5$  min in four of five children) in 23% of otherwise healthy children with acute bacterial meningitis due to *H. influenzae* type b. Although we did not determine the concentrations of moxalactam in serum samples from this group of children, in previous investigations we observed the levels in serum after the same dose (50 mg/kg) to be comparable to those in adults (6). In contrast, 0 of 18 children treated for 10 days with ampicillin or chloramphenicol had bleeding times outside the normal range. In addition, platelet aggregation studies were abnormal in both groups at the end of therapy, which might relate to the infection, the effect of antibiotics, or both. The marked thrombocytosis that was noted in 50% of the chil-

dren at the end of therapy may, in part, explain the normal bleeding times when the platelet aggregation studies were abnormal. Aspirin taken before the admission of patients cannot explain the decrease in platelet aggregation at the end of therapy (11). Thus, platelet function in children, as assessed by bleeding time, may be impaired by moxalactam but not to the same degree as in adults. This study again points out that adverse drug effects noted in adults cannot be routinely assumed to occur to the same degree in children.

Prolonged bleeding times and abnormal platelet aggregation studies at the time of admission were noted in some of the children with *H. influenzae* type b meningitis, suggesting that alteration of platelet function may be associated with *H. influenzae* type b infection, a finding not previously described.

Saba et al. (13) found that endotoxin from a variety of microorganisms (*Salmonella* sp., *Serratia marcescens*, and *Escherichia coli*) inhibits human platelet aggregation induced by ADP, collagen, or arachidonic acid and blocks the release of <sup>14</sup>C-serotonin from platelets, suggesting that endotoxin could inhibit aggregation by a direct action on platelets. Such a mechanism might also explain the altered platelet function in patients with *H. influenzae* type b meningitis. The clinical significance of this platelet defect is unknown because none of these children had serious bleeding.

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